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(54) Penetration enhancement with binary system of cell envelope disordering compounds and lower alcohols.

(57) Penetration-enhancing pharmaceutical compositions for topical transepidermal and percutaneous application are disclosed. These compositions are made up of a safe and effective amount of an active pharmaceutical permeant contained in a novel penetration-enhancing vehicle comprising, (i) a cell-envelope disordering compound; and (ii) a lower alkanol selected from the group consisting of ethanol, propanol and isopropanol and mixtures thereof. The weight ratio of cell-envelope disordering compound to lower alkanol is between about 50:1 to 1:50 and preferably between about 9:1 and 1:9. Preferred cell-envelope disordering compounds are oleic acid, oleyl alcohol, glycerol oleates, methyl oleate, methyl laurate and mixtures thereof. The novel penetration enhancer vehicles are non-irritating to the skin and enhance the penetration of a broad spectrum of pharmaceutical permeants including hydrophilic salts.

EP 0 267 617 A1

PENETRATION ENHANCEMENT WITH BINARY SYSTEM OF CELL ENVELOPE DISORDERING COMPOUNDS AND LOWER ALCOHOLS

This invention relates to compositions which enhance the penetration of pharmaceutically-active agents through the integument. More particularly, this invention relates to binary combinations of penetration enhancers which facilitate percutaneous and transepidermal delivery of a broad range of pharmaceutically-active agents.

The resistance of the skin to being penetrated by pharmaceutically-active agents is well documented. As compared to mucosal tissues, the stratum corneum is compact and highly keratinized. The lipids and proteins of the stratum corneum, although relatively thin, is compact and quite impermeable. Such impermeability of the skin is highly essential to the well being of a living organism in that it serves as a barrier to the ingress of pathogens and toxic materials, and the egress of physiologic fluids.

The impermeability of pharmaceutical agents through the skin is due to the nature of the very thin stratum corneum layer which is only 10-15 cells, i.e. about 10 microns thick. This layer is formed naturally by cells migrating toward the skin surface from the basal layer. Cells slowly move from the basal layer to the surface where they are sloughed off. As they progress toward the surface they become progessively more dehydrated and keratinized.

Because of the advantages of dermal application of pharmaceutically-active agents, various penetration enhancers have been sought. A penetration enhancer is one or more compounds which alter the skin as a barrier to increase the flux of a desired pharmaceutical permeant across the skin.

Penetration enhancers have been primarily categorized according to their ability to enhance permeant flux via three pathways. The first is the continuous polar or aqueous pathway composed of proteins. It is though that solvent swelling or protein conformational changes provide the key to altering the penetration of the polar pathway. Surfactants alter the transport of polar permeant molecules to a much greater extent than the transport of nonpolar permeants. Solvents such as DMSO, 2-pyrrolidone and dimethylformamide can swell the stratum corneum to also enhance the polar pathway.

The second pathway is a continuous non-polar pathway consisting of lipids. The key to altering this pathway appears to be fluidizing the lipids which, in the stratum corneum, appear to be crystalline. Solvents such as DMSO, 2-pyrrolidone, and dimethylformamide, previously mentioned also appear able to solubilize or fluidize lipids. Other solvents include diols such as glycerol and propylene glycol.

The third pathway is a heterogeneous polar-nonpolar multilaminate of lipids and proteins. Binary vehicles appear best suited to act as enhancers on this multilaminate pathway. Prior art binary systems consist of a particular category of a polar solvent combined with a variety of compounds generally referred to as "cell-envelope disordering compounds".

U. S. Patent 4,537,776, Cooper, issued August 27, 1985 contains an excellent summary of prior art and background information detailing the use of certain binary systems for permeant enhancement. Because of the completeness of that disclosure, the information and terminology utilized therein are incorporated herein by reference. That patent teaches using a binary system wherein N-(2-hydroxyethyl)pyrrolidone is used as the solvent and the cell-envelope disordering compounds are selected from the group consisting of methyl laurate, oleic acid, oleyl alcohol, moloolein, myristyl alcohol and mixtures thereof.

Similarly, European Patent Application 43,739, published January 13, 1982, teaches using selected diols as solvents along with a broad category of cell-envelope disordering compounds for delivery of lipophilic pharmacologically-active compounds. This reference also teaches that cosmetically acceptable solvents may also be combined with permeant and the diol and cell-envelope disording compounds provided the solvent evaporates rapidly and completely to leave only the active components of the composition at the site of application. The acceptable solvents are stated to be ethanol or isopropanol. Because of the detail in disclosing the cell-envelope disordering compounds and the diols, the disclosure of European Patent Application 43,738 is also incorporated herein by reference.

Most of the cell-envelope disordering compounds mentioned in these publications are unsaturated lipid components having polar head groups.

A binary system for enhancing metoclopramide penetration is disclosed in UK Patent Application GB 2,153,223 A, published August 21, 1986 and consists of a monovalent alcohol ester of a C8-32 aliphatic monocarboxylic acid (unsaturated and/or branched if C18-32) or a C6-24 aliphatic monoalcohol (unsaturated and/or branched if C14-24) and an N-cyclic compound such as 2-pyrrolidone, N-methylpyrrolidone and the like. It is postulated that the N-cyclic compound serves a solvent function which carries the active agent whereas the esters or alcohols serve as adjuvants to open up the stratum corneum, i.e. as cell-envelope disordering compounds.

In referring to the epidermal permeability of lower alkanols, Drug Delivery Systems, Characteristics and Biomedical Applications, Oxford University Press, NY, 1981, edited by R. L. Juliano, teaches at page 159 that simple alcohols through n-butanol have epidermal permeabilities no different than that of water. However, Campbell et al, U.S. Patent 4,379,454; Campbell et al, U.S. Patent 4,460,372 and Gale et al, U.S. Patent 4,588,580 refer to the use of gelled ethanol as an enhancer in specialized transdermal or percutaneous drug delivery devices.

From the above cited art and incorporated disclosures, it is apparent that some binary enhancers favor lipophilic permeants. There appears to be no recognition of an enhancer system that favors the penetration of salts and other hydrophilic permeants. Moreover, those binary systems containing diols and N-cyclic solvents may cause considerable skin irritation even at low concentrations. However, diols or N-cyclic solvents are taught to be necessary components of a binary system. In general, simple alcohols are taught to be cosolvents to help bring various mixtures into solution but are to be evaporated rapidly from the skin surface and do not function as penetration enhancers any better than water.

Other patents or publications relating to transdermal administration of active permeants are Cooper, European Patent Application 95,813,A2, published July 12, 1983, entitled Penetrating Topical Pharmaceutical Compositions Containing 9-(2-Hydroxyethoxymethyl)Guanine; Durrant et al, European Patent Application 117,080, published August 29, 1984 entitled Skin Treatment Composition.

The present invention relates to improved compositions and methods for improving the penetration of a broad category of pharmaceutically-active agents which are lipophilic or hydrophilic including salts and which produce little or no skin irritation to human or animal tissue systems. The invention provides penetrating topical compositions based on the use of a pharmaceutically-active agent dissolved in, or admixed with, a penetration-enhancing binary mixture of (a) one or more cell-envelope disordering compounds and (b) a C2 or C3 alcohol.

By employing this binary mixture it has been found that significant penetration of salts and other hydrophilic permeants as well as lipophilic permeants is obtained and that skin irritation often associated with cell-envelope disordering compounds and/or solvents is essentially nonexistent.

The invention is therefore not limited to any specific category or categories of permeants but is inclusive of all therapeutically active compounds and their use which are responsive by being incorporated into the binary mixture as more fully set forth herein.

Also, the invention is drawn to treatment methods by means of which an effective amount of a permeant, combined with the binary mixture, is topically applied to a human or animal subject.

The following definitions, when used and as they apply to the present invention, are consistent with those contained in U.S. Patent 4,537,776.

By "topical administration" or "topical application" is meant directly laying or spreading upon epidermal tissue, especially outer skin or membrane, including the skin or membrane of the oral or vaginal cavities.

By "safe and effective", is meant a sufficient amount of the permeant composition to provide the desired systemic effect and performance, or local activity, or both at a reasonable benefit/risk ratio attendant any medical treatment. Within the scope of sound medical judgment, the amount of permeant used will vary with the particular condition being treated, the severity of the condition, the duration of the treatment, the specific permeant compound employed, its concentration, the condition of the patient, concurrent therapies being administered and other factors within the knowledge and expertise of the patient or the attending physician or other practitioner.

By "toxicologically-or pharmaceutically-acceptable" is meant the pharmaceutical actives (or permeants), as well as the other compatible drugs, medication or inert ingredients which the term describes, are suitable for use in contact with the tissues of humans and animals without undue toxicity, irritation, allergic response, and the like, commensurate with a reasonable benefit/risk ratio.

By the term "comprising" is meant that various other compatible drugs and medicaments, as well as inert ingredients, occlusive agents, and cosmetic vehicles, can be conjointly employed in the compositions and methods of this invention; as long as the critical binary penetration enhancement vehicle and pharmaceutically active permeant are used.

By "afflicted situs" is meant a localized area of pathology, discomfort, infection, inflammation or lesion, and the immediately surrounding area.

By "application situs" is meant a site suitable for topical application with or without the means of a mechanical sustained release device, patch or dressing, e.g. behind the ear, on the arm, back, chest, stomach, leg, top of foot, etc.

By "penetration-enhancing" is meant that the binary penetration enhancing carriers or vehicles of this invention provide marked transepidermal or percutaneous delivery of an incorporated active permeant, when compared to other compositions at equal chemical potential. Equal chemical potential is important since

varying solubilities of drugs in different carrier vehicles will affect their transport across skin. As stated in U. S. Patent 4,537,776, if a drug is soluble in vehicle A to the extent of 24%, and in vehicle B to the extent of 4%, were the compositions to be compared at equal percentage concentration, rather than equal chemical potential, the lower solubility carrier would show a misleading six-fold difference in transport over the more soluble vehicle. Therefore, the simplest way of assuring equal chemical potential for evaluating penetration enhancement is to use saturated solutions or solutions of equal percentage of saturation of active permeants in the various enhancer combinations, e.g. 50% saturated. In the examples used herein, the enhancer combinations are saturated with the active permeant components.

As used herein, all percentages and ratios are by weight of the total composition unless otherwise specified.

The terms "permeant", "active", "pharmaceutical active", "pharmacological active", pharmaceutical agent", "pharmacological agent", "pharmaceutically-, or pharmacologically-active agent", "chemical agent", "therapeutic agent", and "drug", are used interchangeably herein.

The compositions of this invention require, at a minimum, a permeant capable of producing systemic effects, or producing or possessing local activity, in a binary vehicle or carrier comprising a cell-envelope disordering compound and a lower alcohol selected from the group consisting of ethyl alcohol, propyl alcohol or isopropyl alcohol.

The composition may also contain other optional components which enhance their cosmetic appeal or acceptability, i.e., thickeners, pigments, fragrances, perfumes and the like.. The binary penetration combinations are essentially free of skin irritation characteristics. However, a permeant combined with the penetration enhancers may cause some irritation. Therefore, if desired other components which tend to reduce skin irritation may be incorporated into the compositions.

The binary penetration enhancement combinations of the present invention significantly enhance the penetration of a host of pharmaceutically-active permeants including salts. These permeants may be lipophilic or hydrophilic or partially lipophilic or hydrophilic.

The binary combinations comprise one or more cell-envelope disordering compound and a lower alkanol selected from the group consisting of ethanol, propanol and isopropanol.

The cell envelope disordering compounds are known in the art as being useful in topical pharmaceutical preparations. These compounds are thought to assist in penetration by disrupting or disordering the lipid structure of the stratum corneum cell-envelopes. A comprehensive list of these compounds is described in European Patent Application 43,738 published June 13, 1982 which is incorporated herein by reference. Some additions to the structural formulae disclosed therein have been made to include certain glycerol esters. It is sufficient for purposes of this disclosure to state that the cell envelope disordering compounds are encompassed by the formula R-X wherein R is a straight-chain alkyl of about 7 to about 16 carbon atoms, a non-terminal alkenyl of about 7 to about 22 carbon atoms, or a branched-chain alkyl of from about 13 to about 22 carbon atoms, and X is -OH, $-COOCH_3$, $-COOC_2H_5$, $-OCOCH_3$, $-SOCH_3$, $-P(CH_3)_2O$, $-COOC_2H_4OC_2H_4OH$, $-COCH(CHOH)_xCH_2OH$, $-COOCH_2CHOHCH_3$, $-COOCH_2CHCH_2OR^2$, $-(OCH_2CH_2)_m$ OH, OR^2

or -COOR^1, or -CON-R^1, wherein R^1 is -H, $-CH_3$,

$-C_2H_5$,

R^1

$-C_3H_7$ or $-C_3H_4OH$; R^2 is -H, or a non-terminal alkenyl of about 7 to about 22 carbon atoms; and m is 2-6; the ratio of cell envelope-disordering compound: C_2 or C_3 alcohol compound being in the range of from about 1:50 to about 50:1 by weight.

Numerous specific cell envelope disordering compounds are listed in European Patent Application 43,738. The cell envelope disordering compounds preferred for use in combining with ethanol, propanol or isopropanol to form penetration enhancing compositions of the present invention include oleic acid, oleyl alcohol, glycerol trioleate, glycerol dioleate, glycerol monoleate (monoolein) methyl oleate and methyl laurate and mixtures thereof. Particularly preferred are oleic acid and glycerol dioleate and mixtures thereof.

Binary mixtures of a C_2-C_3 alcohol and any of the above referenced cell-envelope disordering compounds, in a weight:weight ratio of alcohol to cell-envelope disordering compound of about 50:1 to about 1:50, provide significantly enhanced penetration for the permeants described herein. A weight:weight ratio of alcohol:cell-envelope disordering compounds of from about 1:9 to 9:1 is preferred.

The compositions of the invention typically contain from about 40 to 99.99%, and preferably about 70 to 99.9%, by weight of the overall composition, of the penetration enhancing binary mixture of C_2 or C_3 alcohol and the cell-envelope disordering compound employing the ratios described above. The exact percentages may be readily determined by one having ordinary skill in the art. All that is required is that an effective amount of the active permeant be incorporated into the penetration enhancing composition with or without

being combined with other ingredients.

The binary penetration enhancers of the present invention may be formulated to incorporate a broad range of pharmaceutically-active permeants. One of the distinct advantages of these enhancer combinations is that they function to enhance penetration of both lipophilic and hydrophilic permeants including salts and are virtually free from skin irritation effects. The compositions of this invention may be utilized in delivering active permeants to the "target" areas as mentioned in U. S. Patent 4,537,776, i.e. (1) at the surface of the skin; (2) in the stratum corneum itself; (3) in the viable epidermis and upper dermis, just below the stratum corneum; (4) in the various glands and structures in and beneath the dermis (e.g., subcutaneous adipose, dermal vasculature); and/or (5) the general system (i.e. systemic effects).

In view of this, the invention is not limited to any specific type or class of active permeants. Based on the parameters contained herein it is within the ability of one having ordinary skill in the art to determine which permeants can be utilized. Some routine experimentation or testing may be required to determine optimum conditions such as exact concentrations of permeants, ratios of cell-envelope disordering compounds to alcohols, and the like. Also, some permeants may work best with one particular class of cell-envelope disordering compounds and/or alcohols. The screening of all possible combinations and ratios of permeants, cell-envelope disordering compounds and C_2 and C_3 alcohols has not been attempted.

However, based on the formulatoin of a representative sampling of diverse active permeants, it is apparent that the binary combination of a cell-envelope disordering compound and a C_2 or C_3 alcohol will function to enhance the penetration of a broad spectrum of pharmaceutically-active permeants. Such agents include, without limitation, those mentioned in U. S. Patent 4, 537,776 such as antimicrobials, antibacterials, antibiotics, antimycobacterials, antimalarials, antiamebics, anthelmintics, antifungals, antivirals, neoplastic agents, agents affecting the immune response, blood calcium regulators, peptide and protein hormones, male sex hormones, female sex hormones, agents useful in glucose regulation, anticoagulents, antithrombotics and hemostatics, antihyperlipidemic agents, cardiac drugs, thyromimetic and antithyroid drugs, adrenergics, antihypertensive agents, cholinergics, anticholinergics, antispasmodics, antiulcer agents, skeletal and smooth muscle relaxants, histamine H_2-receptor agonists and antagonists, prostaglandins, general inhibitors of the allergic response, antihistamines, local anesthetics, analgesics, antitussives, sedative-hypnotic agents, anticonvulsants, antipsychotics, anti-anxiety agents, antidepressant agents, anorexigenics, non-steroidal anti-inflammatory agents, steroidal anti-inflammatory agents, bone-active agents, antiarthritics, vitamins, diagnostic agents and sunscreens. These agents can be used for systemic effect, local activity, or both, as appropriate. Examples of pharmaceutically-active permeants are well-known in the art and can be found listed in sources identified in U. S. Patent 4,537,776 as well as others. For example, active agents, in approved commercially available formulations, their recommended dosages, adverse reactions, side effects and the like are listed in the annual publication of the Physicians' Desk Reference, published by Medical Economics Company, a division of Litton Industries, Inc.

The pharmaceutically-active permeants may be used in the compositions and methods of the present invention at any safe and effective level, or in any safe and effective amount. Dosages will obviously be a function of various variables, such as how active the agent is, how soluble it is in the penetration enhancing composition, how often it is to be applied, whether the use is to be topical (applied to the "afflicted situs") or systemic (applied to the "application situs"), whether two or more active permeants are to be combined, the particular patient being treated, and the like. In any event the dosage will be the smallest that will achieve the desired result and the period of administration will be as short as possible to attain this result.

In general, dosages and means of application as taught in U.S. Patent 4,337,776 are appropriate to the present invention. Levels of active permeants may vary from about 0.01% to about 40% by weight of the total composition with levels of from about 0.01 to 30% being preferred. Levels from about 0.05 to 15% being especially preferred and levels of from about 0.1 to 10% being most especially preferred for some active permeants. However, for some active permeants it may be required to use more or less than stated above to attain the desired results. Hence, the invention is not directed to any particular amount of active ingredient as long as it is safe and effective.

A compendium of active permeants is contained in U.S. Patent 4,537,776 and published European Patent Application 43,738 and incorporated herein by reference. However, for purposes of illustration a more concise listing of active agents follows.

Typical antihypertensive agents which may be utilized include, without limitation, minoxidil, nadolol, pargyline, pindolol, propanolol, reserpine, timolol, trimethaphan, metoprolol, hydrochlorothiazide, hydralazine, furosemide, clonidine and chlorthalidone.

Diuretics include, without limitation, benzthiazide, buthiazide, cyclopenthiazide, cyclothiazide, metolazone, triamterelene, chlorazanil, clazolimme, and hydroflumethiazide.

Exemplary of anorexigenics are, without limitation, amphetamine, methamphetamine, chlorphentermine, clortermine, phentermine, phendimetrazine, mazindol, oxazoline, and phenoxalbyleneamine.

Fungistatic and funicidal agents encompass, without limitation, thiabendazole, chloroxine, fungimycin, griseofulvin, chlordantoin, salicylic acid, nystatin, clotrimazole, fezatione, sodium pyrithione, amphotericin B, 5-fluorocytosine, haloprogin, vitampin, and pimaricin.

A broad range of analgesics may be utilized including without limitation, morphine, codeine, heroine, methadone, thebaine, orpiarine, buprenorphine, morphinans, benzomorphans, acetaminophen, butorphanol, diflunisal, fenoprofen, fentanyl, fentanyl citrate, hydrocodone, ibuprofen, oxymorphone, pentaxicine, naproxen, nalbuphine, mefenamic acid, meperidine and dihydroergotamine.

Exemplary antiussive agents include, without limitation, diphenhydramine, guaifenesine, hydromorphone, ephedrine, phenylpropanolamine, theophylline, codeine, noscapine, levopropoxyphene, carbetapentane, chlorpehndianol and benzonatate

Among the sedatives which may be utilized are, without limitation, chloralhydrate, butabarbital, alprazolam, amobarbital, chlordiazepoxide, diazepam, mephobarbital, secobarbital, diphenhydramine, ethinamate, flurazepam, halazepam, haloperidol, prochlorperazine, oxazepam, and talbutal.

Examples of cardiac drugs are, with limitation, quinidine, propanolol, nifedipine, procaine, dobutamine, digitoxin, phenytoin, sodium nitroprusside, nitroglycerin, verapamil HCl, digoxin, nicardipine HCl, and isosorbide dinitrate.

Antimicrobial agents are includive of, without limitation, erythromycin, sulfonamide, lincomycin, clindamycin, tetracycline, chlortetracycline, demeclocycline, doxycycline, and methacycline.

Examples of useful antibacterial agents are, without limitation, phenols, hydroxy benzoic acid, hydroxy quinoline, nitrofuran, nitroimidazoles, oxolinic acid, actinomycetin, bacitracin, tyrothricin, kanamycin, neomycin and chloramphenicol.

Steroidal anti-inflammatory agents are illustrated by, without limitation, triamcinolone acetonide, beclomethasone dipropionate, hydrocortisone acetate, fluocinolone acetonide, betamethasone valerate, prednisolone, prednisone, methyl prednisolone and paramethasone.

Inclusive of non-steroidal anti-inflammatory agents are acetyl salicylic acid, fenoprofen calcium, ibuprofen, indomethacin, meclofenamate sodium, mefenamic acid, naproxen sodium, phenylbutazone, and oxyphenbutazone.

Anti-emetics are illustrated by, without limitation, thiethylperazine, metoclopramide, cyclizine, meclizine, prochlorperazine, doxylamine succinate, promethazine, triflupromazine, and hydroxyzine.

Exemplary amino acid, peptide and protein hormones include, without limitation thyroxine, growth hormone (GH), interstitial cell stimulating hormone (ICSH), follicle-stimulating hormone (FSH), thyrotropic hormone (TSH), andrenocorticotropic hormone (ACTH), vasopressin and their active degradation products.

Some products may have sufficiently high molecular weights that absorption through the stratum corneum or mucous membranes may be difficult. Therefore, the invention is applicable only to those hormones which have molecular weights and stereoconfigurations which will allow passage through the skin.

Female sex hormones which can be used include, without limitations, estradiol, diethylstilbestrol, conjugated estrogens, estrone, norethindrone, medroxyprogesterone, progesterone, and norgestrel.

Typical male sex hormones which may be utilized may be represented by, without limitation, testosterone, methyltestosterone, and fluoxymesterone.

The above listed active permeants may, along with others not specifically disclosed, be used separately or in combination according to the treatment regimen desired.

Preferred categories of active permeants include anti-hypertensive agents, cardiac drugs, analgesics, sedative-hypnotic agents, anti-anxiety agents, steriodal anti-inflammatory agents, non-steroidal anti-inflammatory agents, male sex hormones, and female sex hormones. Those active permeants specifically listed above under each category are particularly preferred.

The components of this invention are inclusive of the active permeants combined with the binary penetration enhancing mixture of cell-envelope disordering compounds and C2 and C3 alcohols. It is contemplated that compositions containing only these ingredients will be sufficient in most instances to obtain the desired results. However, in preparing formulations for actual use, it may be desirable to add other components such as excipients, dyes, perfumes, fragrances, opacifiers, thickening agents, preservatives, anti-oxidents, gelling agents, surfactants and stabilizers. For example, when forming gels or cremes, it may be desirable to add significant amounts of water, i.e. up to 50% in some cases for gels. Such materials, when added, should not unduly interfere with the penetration enhancement of these compositions. Such formula modifications to improve cosmetic acceptability are well within the skill of workers in the art and do not form part of the present invention.

In any form of medical practice, there are many variables which affect the particular treatment regimen.

In that regard, the final diagnosis and treatment is left to the expertise of the practitioner and patient. As previously stated, in clinical practice, it is the goal that the dosage of any active permeant be as small as possible to achieve the result desired and that the duration of the administration of the permeant be as short as possible. To attain these conditions, it is imperative that the amount of active ingredient utilized is a safe and effective amount whether applied to an afflicted situs or an application situs. When local treatment is desired, the compositions are applied to the afflicted situs. When systemic treatment is desired, the compositions are applied to an application situs, preferably from a sustained release device such as a patch, bandage, web, film or the like. When both local and systemic treatments are indicated, the compositions can be applied at both the afflicted situs and application situs, or both. The selection of active permeant or combination or permeants, particular penetration enhancement combination and the like are necessarily left to the skill of the practitioner provided the parameters outlined herein are followed.

The dosage, rate of application, place of application, and other treatment parameters are generally outlined in U.S. Patent 4,537,776 and are incorporated herein by reference rather than being repeated. What is a safe and effective amount of any ingredient will obviously depend upon the active ingredient being used, the site of application, the effectiveness of the penetration enhancer and other parameters outlined herein.

A practitioner being skilled in the art will be able to determine the application parameters of each specific formulation based on the needs of each patient.

The following examples demonstrate the penetration enhancement which is obtained by the binary cell envelope disordering compounds-lower alkanol compositions. In making these tests human skin consisting of heat-separated abdominal epidermis, taken at autopsy, was placed in a standard Franz diffusion apparatus in a horizontal position between a lower, capped diffusion cell and an upper open cell. A normal saline solution was added to the lower diffusion cell in contact with the subcutaneous side of the skin, and the test composition, consisting of a saturated solution of an active drug being monitored formulated in the binary penetration enhancer, was added to the diffusion cell in contact with the upper or epidermal side of the skin.

The cell assembly was kept in a constant-temperature room at about 37 degrees C. At predetermined intervals, the diffusate from the cell on the subcutaneous side of the skin was withdrawn and the amount of drug in the diffusate was measured using standard analytical techniques. Each test was run on a separate skin sample. In each case the amount of active drug used was that required to form a saturated solution. The results are reported in terms of flux, [mcg/cm2/day] or relative flux.

EXAMPLE I

To show the penetration enhancement effects of the binary cell envelope disordering compound-lower alkanol compositions are applicable to active agents inclusive of hydrophilic, salts and hydrophobic agents the following compositions were tested.

Flux [mcg/cm2/day]

Test No.	Active Ingredient	Propylene Glycol	Glycerol Dioleate(GDO) (80:20 w/w)	Ethanol/GDO
I-A	Estradiol	14.9	14.3	20.9
I-B	Na-Salicylate	138.6	6,626.0	13,696.4
I-C	Ara-A	0.44	0.48	3.98

The combination of ethanol and GDO shows substantial penetration enhancement effects as compared to a diol (propylene glycol) or GDO alone for all three active agents.

EXAMPLE 11

A series of tests similar to Example I were conducted utilizing a greater variety of active agents with various component combinations forming penetration enhancement systems which were directly compared with individual components making up the systems as follows:

FLUX [mcg/cm2/day]

Test No.	SYSTEM(%w/w)	Estradiol HCl	Prednisilone Salicylate	Propranolol HCl	Minoxidil Sodium	ENHANCEMENT
	40% OA					

II-A 40% GDO
75.6 915.7
1,216.0
383.6
12,838.0
20% EtOH

80% OA
II-B 20% EtOH
21.2 462.0
889.0
303.0
22,905.0

80% GDO
II-C 20% EtOH
48.6 571.0
767.0
197.0
12,541.0

95% PG
II-D 5% OA
120.1 164.0
2,259.0
1,155.0
834.0

II-E 100% OA
31.8 291.0
258.0
221.5
18,349.0

II-F 100% EtOH
18.7 81.0
45.0

23.4
1,094.0

II-G 100% PG
2.6 5.0
25.0
14.6
231.8

II-H 100% GDO
12.1 92.0
257.0
62.1

EtOH=Ethanol
PG=Propylene Glycol
GDO=Glycerol Dioleate
OA=Oleic Acid

The penetration enhancer composition utilized in Test II-D is taught in the prior art and shown in Example XIV of European Patent Application 43,736 and generally provides for excellent skin penetration enhancement. However, as shown in following Example VI, this combination of oleic acid and propylene glycol causes severe skin irritation. The penetration enhancement systems of Tests II-A, II-B and II-C, with minor exceptions, showed across the board improvement in penetration enhancement over the individual components used alone and generally greater than additive enhancement effects which one would expect when combining these ingredients.

EXAMPLE III

Following the procedure and penetration enhancement systems of Example II, the relative flux of haloperidol as active agent was determined. The results are as follows:

Test No.	SYSTEM (%w/w)	ENHANCEMENT RELATIVE FLUX Haloperidol
III-A	40% OA 40% GDO 20% EtOH	19.1
III-B	80% OA 20% EtOH	10.8
III-C	80% GDO 20% EtOH	21.7
III-D	95% PG 5% OA	22.4
III-E	100% OA	5.2
III-F	100% EtOH	5.1
III-G	100% PG	1.0
III-H	100% GDO	12.2

EtOH=Ethanol
PG=Propylene Glycol
GDO=Glyceral Dioleate
OA=Oleic Acid

It is evident from the above that the combinations of glycerol dioleate and/or oleic acid with ethanol provide penetration enhancement similar to that obtained with propylene glycol and oleic acid and, as will subsequently be demonstrated, does not possess the skin irritation properties of propylene glycol-oleic acid combinations. The enhancement obtained by combining GDO and oleic acid cell-envelope disordering agents with ethanol was far greater than that obtained utilizing the individual components alone.

EXAMPLE IV

To show the efficacy of other cell-envelope disordering compounds in combination with lower alkanols as penetration enhancers, a series of tests were run with propanolol as the active agent. The procedure as outlined in the above examples was followed to determine flux. All enhancer combinations consisted of 75% weight of a cell-envelope disordering compound and 25% weight isopropyl alcohol (i-PrOH). The results are as follows:

ENHANCEMENT FLUX
Test No.
SYSTEM (75% w/25%w)
[mcg/cm2/day]
IV-A GDO + i-PrOH
1,814.0
IV-B Methyl Laurate + i-PrOH
5,534.0
IV-C Lauryl Oleate + i-PrOH
571.0
IV-D Methyl Vaccenate + i-PrOH
408.0
IV-E Cis-5-Decenyl Acetate + i-PrOH
5,534.0

Higher Alcohols IV-F Oleyl Alcohol + i-PrOH
4,553.0
IV-G Hexadecenol + i-PrOH
7,055.0
IV-H Dodecanol + i-PrOH
5,461.0
IV-I Vacenyl Alcohol + i-PrOH
6,481.0
IV-J Decanol + i-PrOH
7,102.0
IV-K Octanol + i-PrOH
6,852.0
IV-L Oleic Acid + i-PrOH
860.0
IV-M Petroselenic Acid + i-PrOH
856.0
IV-N Linoleic Acid + i-PrOH
2,358.00

IV-O Linolelaidic Acid + i-PrOH
1,384.0
IV-P Linolenic Acid + i-PrOH
1,204.0
IV-Q Vaccenic Acid + i-PrOH
673.0

While there is no direct comparison utilizing the cell-envelope disordering components of the enhancement combination alone, it has been previously shown that the combinations of enhancers as shown in Tests IV-A and IV-L, utilizing ethyl alcohol instead of isopropyl alcohol, show marked penetration enhancement of active ingredients. Using Tests IV-A and IV-L as the standards, the other cell envelope disordering components, with few exceptions, show comparable or superior penetration enhancement of propranolol.

EXAMPLE V

Again, following the procedure of the preceding examples, a series of tests utilizing glycerol dioleate and/or oleic acid as cell-envelope disordering components combined with isopropyl alcohol as penetration enhancers, were performed using propranolol HCl and testosterone as active agents. Results are as follows:

ENHANCEMENT		
FLUX		
ACTIVE AGENT		
Test No.		
SYSTEM (%w/w)		
[mcg/cm2/day]		
Skin Sample #1		
V-A	100% GDO	
448.8		
Propranolol HCl		
V-B	100% i-PrOH	
67.2		
Propranolol HCl		
	80% GDO	
V-C	20% i-PrOH	
1,000.8		
Propranolol HCl		
Skin Sample #2		
V-D	100% GDO	
120.0		
Testosterone		
V-E	100% OA	
144.0		
Testosterone		
	80% OA	
V-F	20% i-PrOH	
456.0		
Testosterone		

		80% OA
	V-G	10% i-PrOH
	912.0	
	Testosterone	
		10% GDO

Skin Sample #3

V-H		100% A
	76.8	
Testosterone		
		80% OA
V-I		20% i-PrOH
374.4		
Testosterone		
		80% GDO
V-J		20% i-PrOH
384.0		
Testosterone		

i-PrOH=Isopropanol
GDO=Glycerol Dioleate
OA=Oleic Acid

The above show that enhancers consisting of both cell-envelope disordering compounds and isopropanol are clearly superior to the individual components used separately.

EXAMPLE VI

The following test was conducted in order to show that skin penetration enhancers, used in the above examples to facilitate the passage of medicinal compounds through the skin and consisting of combinations of cell-envelope disordering agents combined with a lower alkanol, produce less skin irritation and sensitization than prior art penetration agents consisting of a cell-envelope disordering compound and a diol.

Twenty four healthy adults (sixteen females and eight males) between the ages of 18-65 were selected for the test. Each subject was selected without regard to race or sex. However, each subject was required to be in good health and meet required criteria regarding allergies, skin cancer, medications, recent surgery, etc.

Eight different enhancer compositions (Test Substances I through VIII) were prepared as follows (ingredients reported in % w/w):

I. Propylene glycol: Oleic Acid (85:5).
II. Glycerol dioleate:Ethanol (80:20).
III. Glycerol dioleate:Ethanol (20:80).
IV. Glycerol dioleate:Oleyl alcohol:Ethanol (40:40:20).
V. Glycerol dioleate:Methyl laurate:Ethanol (40:40:20).
VI. Glycerol dioleate:Glycerol formal:Ethanol (70:10:20).
VII. Methyl laurate:Isopropenol (75:25).
VIII. Glycerol dioleate:Oleic acid:Ethanol (70:10:20).

Test solutions were prepared and stored at room temperature until used. When ready for use 150 micro liters of test solution was placed on an adhesive bandage patch consisting of a 3/4 inch square nonwoven cotton pad, Webril (TM) (Kendall Corporation) which retained the test substance, backed by a 1.5 inch square of blenderm type tape (3M Company) to hold the pad onto the surface of the skin. The patches were individually packaged with a peeloff backing.

The backing was peeled off and the test solution applied to the patch. The test area was cleaned with a gauze pad saturated with 95% ethyl alcohol. The patches were then applied to the lateral surface of one upper arm of the subject in a designated sequence to eliminate position and order grading bias.

The best subjects were divided into two application groups (Group A and Group B) of twelve subjects each. Each group was further subdivided into four groups each containing three subjects. Each subject in Group A was treated with test Substances I, II, III and IV and each subject in Group B was treated with test Substances V, VI, VII and VIII. The positioning of substances was the same in each subgroup, but the positioning varied from one subgroup to another according to a randomization code.

The test consisted of nine 24 hour patch exposure (induction period) to the same test site of each subject with a 24 to 48 hour rest period between each exposure. About two weeks after the last induction patch was applied, the original test site and an alternate test site were challenged with a 24 hour patch exposure to the test material.

Each subject was instructed to keep all patches as dry as possible and to remove and discard them after approximately 24 hours. The patch area could be cleaned in a normal manner after removal but the subjects were cautioned not to swim when the patches were in place. There were no bathing or showering restrictions.

Induction patches were applied on Monday, Wednesday and Friday for the first three weeks of the test. The test sites were scored using an artificial light source to illuminate the patch area prior to the application of each new patch during the induction tests with a final reading being taken on the Monday following the ninth application. Two weeks after the final reading of the induction tests, challenge patches were applied simultaneously to both the original (at the original sites) and opposite arms (in a similar position) of each subject. These patches were worn for 24 hours and then discarded. The challenge test sites were graded on the second and fourth days following their application.

Test sites were scored as follows: 0 = no visible reaction; 1 = mild reaction, erythema; 1E = mild erythematous reaction with papules and/or edema; 2 = moderate reaction, erythema; 2E = moderate erythematous reaction with papules and/or edema; 3 = strong reaction, erythema; 3E = strong erythematous reaction with marked edema, papules and/or few vesicles, 4 = severe reaction with erythema, edema, papules and vesicles (may be evidence of weeping); 5 = bullous reaction; [S] = reaction spread beyond patch area: and N9G = No 9th induction grade. Gradings containing two numbers, e.g. 1/1E, are readings from two application sites when skin irritation at the initial test site required the moving of test patches from one test site to another.

The patch site grades are as follows:

Test Substance - I

Subject Drug Number	Induction Grades 1	2	3	4	5	6	7	8	9	Challenge Grades Orig 1	Alt 1	Orig 2	Alt 2
01	1	0	1	1	1	1	1E	1/1	1/1E	1	1	1	1
02	1	1	0	1	1	1E	2E	1E/0	1/3E	2E	2E	3E	3E
03	1	1	1E	1E(S)	1/1E	3E(S)/2E(S)	2E/1	1E/1	1/1	5(S)	4(S)	3E	2(S)
04	0	1	1	1	1E(S)	1/1E	1E/1	2E/1	1/1	3E	2E	2E	2
05	1E	1	2E	1E/3E(S)	2E/1E	1/4	1/2E	1/1	1/1E	1	0	1	0
06	1	1	1E	2E(S)	2/2E	3E/2E	3E/3	2/2	N9G	*	*	*	*
07	1	1	1	1	1	1E	2	1/1E	1E/2E	2E	2E	1E	1E
08	1	1	1	1	1	1	1E	1/1E	1/2E	2E	3	1E	2E
09	0	0	1	1	1	1E	2E	1E/1E	1/2E	3E	3E	3E	3E
10	1	1	1	1	1	1	2E	0/1E	1/3E	5(S)	4	4	2E
11	1	1	1	1	1E	2E	2/5	1/3E	1/1E	2E	2E	1E	1E
12	1E	1	1	1	2	1/2E	2/1E	1E/1E	1/1	2E	3E	1E	2E

* Patch not applied.

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Test Substance - II

Subject Drug Number	Induction Grades									Challenge Grades			
	1	2	3	4	5	6	7	8	9	Orig 1	Alt 1	Orig 2	Alt 2
01	0	0	0	0	0	0	0	0	0	0	0	0	0
02	0	0	0	0	0	0	0	0	0	0	0	0	0
03	0	0	0	0	0	0	0	0	0	0	0	0	0
04	0	0	0	0	0	0	0	0	0	0	0	0	0
05	0	0	0	0	0	0	0	0	0	*	*	*	*
06	0	0	0	0	1	1	1	1	NSG	*	*	*	*
07	0	0	0	0	0	0	0	0	0	0	0	0	0
08	0	0	0	0	0	0	0	0	0	0	0	0	0
09	0	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0	0

* Patch not applied.

Test Substance - XII

Subject Group Number	Induction Grades								Challenge Grades			
	1	2	3	4	5	6	7	8	9	Orig 1	Alt 1	Orig 2	Alt 2
01	0	0	0	0	0	0	0	0	0	0	0	0	0
02	0	0	0	0	0	0	1E	1	1	0	0	0	0
03	0	0	0	0	0	0	0	0	0	0	0	0	0
04	0	0	0	0	0	0	0	0	0	0	0	0	0
05	0	0	0	0	0	0	0	0	0	0	*	0	*
06	0	0	0	0	1	1	1	0	NPG	*	*	*	*
07	0	0	0	0	0	0	0	0	0	0	0	0	0
08	0	0	0	0	0	0	0	0	0	0	0	0	0
09	0	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0	0

* Patch not applied.

Test Substance - IV

Subject Drug Number	Induction Grades									Challenge Grades			
	1	2	3	4	5	6	7	8	9	Orig 1	Alt 1	Orig 2	Alt 2
01	0	0	0	0	0	0	0	0	0	0	0	0	0
02	0	0	0	0	0	0	0	0	0	0	0	0	0
03	0	0	0	0	0	0	0	0	0	0	0	0	0
04	0	0	0	0	0	0	0	0	0	0	0	0	0
05	0	0	0	0	0	0	2E	0	0	*	*	*	*
06	0	0	0	0	1	1E	2E/1	1/0	3SG	*	*	*	*
07	0	0	0	0	0	0	0	0	0	0	0	0	0
08	0	0	0	0	0	0	0	0	0	0	0	0	0
09	0	0	0	0	0	0	0	0	0	0	0	0	0
10	0	0	0	0	0	0	0	0	0	0	0	0	0
11	0	0	0	0	0	0	0	0	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0	0	0	0	0

* Patch not applied.

Test Substance - V

Subject Drug Number	Induction Grades									Challenge Grades			
	1	2	3	4	5	6	7	8	9	Orig 1	Alt 1	Orig 2	Alt 2
13	0	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	1	0	0	0	0	1	0	0	0
15	0	0	0	0	0	0	0	0	0	0	0	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	0	0	0	0	0
19*	0	0	0	0	0	-	-	-	-	-	-	-	-
20	0	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	0	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	0	0	0	0	0

* Subject discharged due to viral illness

Test Substance - VI

Subject Drug Number	Induction Grades									Challenge Grades			
	1	2	3	4	5	6	7	8	9	Orig 1	Alt 1	Orig 2	Alt 2
13	1	0	0	0	0	0	0	0	0	0	1	0	1
14	0	0	0	0	1	1	1	1	1	1	1	0	0
15	0	0	0	1	0	0	1	0	0	1E	1E(S)	1E	1
16	0	0	0	0	1	1	0	0	1	0	0	0	0
17	0	0	1	0	0	1	0	0	1	0	0	0	0
18	0	1	1	1	1	1	1	0	1	1E	1E	1	2
19*	0	0	±	±	±	–	–	–	–	–	–	–	–
20	0	0	0	0	0	0	1	1	1	0	1	0	0
21	0	0	0	0	0	0	0	0	1	1	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	1	0	0	0	0	0	0	0
24	0	1	1E	2E	1/1E	1/2E	2E/1E	2/1	1/1	1E	1E	1E	1E

* Subject discharged due to viral illness

Test Substance - VII

Subject Drug Number	Induction Grades									Challenge Grades			
	1	2	3	4	5	6	7	8	9	Orig 1	Alt 1	Orig 2	Alt 2
13	0	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	1	0	0	0	0	1	1
15	0	0	0	0	0	0	0	0	0	1	1	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	0	0	0	0	0	0	0
18	0	0	0	0	0	0	0	1	1	0	0	0	0
19*	0	0	0	0	0	0	-	-	-	-	-	-	-
20	0	0	0	0	0	0	0	0	0	0	0	0	0
21	0	0	0	0	0	0	0	0	0	1	0	0	0
22	0	0	0	0	0	0	0	0	0	0	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	1	0	0	0	0

* subject discharged due to viral illness

Test Substance - VIII

Subject drug Number	Induction Grades 1	2	3	4	5	6	7	8	9	Challenge Grades Orig 1	Alt 1	Orig 2	Alt 2
13	0	0	0	0	0	0	0	0	0	0	0	0	0
14	0	0	0	0	0	0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0	0	0	0	1	0	0
16	0	0	0	0	0	0	0	0	0	0	0	0	0
17	0	0	0	0	0	0	1	0	0	0	0	0	0
18	0	0	0	0	0	0	0	0	1	0	-	0	-
19*	0	0	0	0	0	0	-	-	-	-	-	-	-
20	0	0	0	0	0	1	1E	1E	1	0	0	0	0
21	0	0	0	0	0	0	0	0	1	0	0	0	0
22	0	0	0	0	0	0	0	0	0	1	0	0	0
23	0	0	0	0	0	0	0	0	0	0	0	0	0
24	0	0	0	0	0	0	0	0	1	0	0	0	0

* Subject discharged due to viral illness

Because of severe reaction caused by Test Substance #1, no induction patches were applied to Subject No. 5 at the last two induction applications. At challenge, patches free of any test substance were applied to selected sites to evaluate the Subject's reaction to the tape and the possible exacerbation by the action of the test substances.

On Subject No. 6, severe reaction was observed at Test Substance #1 site after the fifth test induction application which spread to all patch sites. After the sixth test induction application, no patches were applied to any test site for the remainder of the induction period. At challenge, patches containing no test substance were applied to selected sites on both arms of the subject.

The testing investigator's conclusions were that, except for Test Substances 1 and 6, the adverse symptomatology was generally mild in nature and no medical intervention was required. All twelve subjects treated with Test Substance #1 experienced significant skin changes during the induction period. Nine of the subjects also experienced exacerbation of the skin changes following the challenge patch application. One subject treated with Test Substance #6 experienced significant skin changes both during induction and challenge periods. Two subjects displayed mild reactions to Test Substance #6 during induction which became more severe during challenge. Medical intervention in the form of patch relocation or interruption of patch application was necessary for the significant skin responses to Test Substances #1 and #6.

In conclusion, it is evident that Test Substances #2, #3, #4, #5, #7 and #8, all of which are within the scope of the present invention, are substantially free from skin irritation effects. On the other hand, Test Substance #1, from the prior art, and Test Substance #6, which had shown promising penetration

enhancement in preliminary testing, both showed significant skin irritation.

Blood samples taken from all twenty-four subjects before and after testing showed no clinically significant changes in serum prolactin levels.

EXAMPLE VII

The following are exemplary of other compositions which can be formulated within the scope of this invention. However, they are illustrative only and are not intended to define the scope of the invention. The compositions can be conventionally formulated simply by mixing all components thoroughly. In some formulations, exact percentages are given whereas others are expressed by ranges. All compositions are in percent by weight.

FORMULATION VI-A Testosterone 5-15%
Glycerol Dioleate 50-90%
Ethanol 4-45%

FORMULATION VI-B Methadone 10-30%
Glycerol Dioleate 60-80%
Ethanol 10-30%

FORMULATION VI-C Estradiol 0, 1-1.0%
Glycerol Dioleate 60-95%
Ethanol 5-40%

FORMULATION VI-D Ketoprofen 10-20%
Glycerol Dioleate 50-90%
Ethanol 5-40%

FORMULATION VI-E Dihydroergotamine 1-10%
Glycerol Dioleate 50-95%
Ethanol 5-40%

FORMULATION VI-F Nifedapine 2-10%
Glycerol Dioleate 50-95%
Ethanol 5-40%

FORMULATION VI-G Thiethylperazine 1.-5%
Glycerol Dioleate 50-95%
Ethanol 5-50%

FORMULATION VI-H Metoclopramide 10-15%
Glycerol Dioleate 50-90%
Ethanol 5-40%

FORMULATION VI-I Propanolol HCl 5%
Glycerol Dioleate 75%
Ethanol 20%

FORMULATION VI-J Propranolol 20%
Glycerol Dioleate 60%
Ethanol 20%

FORMULATION VI-K Propranolol HCl 5%
Glycerol Monooleate 80%
Ethanol 15%

FORMULATION VI-L Propanolol HCl 5%
Methyl Laurate 75%
Ethanol 20%

FORMULATION VI-M Propranolol 15%
Glycerol Trioleate 65%
Isopropanol 20%

FORMULATION VI-N Fentanyl Citrate 2%
Glycerol Monooleate 78%
Ethanol 20%

FORMULATION VI-O Fentanyl 1%
Glycerol Trioleate 79%
Isopropanol 20%

FORMULATION VI-P Nicardipine 5%
Oleyl Alcohol 75%
Isopropanol 20%

FORMULATION VI-Q Nicardipine HCl 10%
Oleic Acid 10%
Glycerol Dioleate 50%
Ethanol 30%

FORMULATION VI-R Naloxone HCl 10%
Glycerol Monooleate 60%
Oleic Acid 10%
Ethanol 20%

FORMULATION VI-S Naloxone 5%
Glycerol Trioleate 65%
Propanol 30%

FORMULATION VI-T Griseofulvin 5%
Methyl Oleate 75%
Isopropanol 20%

FORMULATION VI-U Griseofulvin 5%
Glycerol Trioleate 65%
Isopropanol 30%

FORMULATION VI-V Fluocinolone Acetonide 1%
Methyl Laurate 79%
Ethanol 20%

FORMULATION VI-W Fluocinolone Acetonide 1%
Glycerol Trioleate 69%
Isopropanol 20%

FORMULATION VI-X Clindamycin 2.5%
Oleyl Alcohol 77.5%
Isopropanol 20%

FORMULATION VI-Y Neomycin Sulfate 5%
Glycerol Monooleate 75%
Ethanol 20%

FORMULATION VI-Z Clonidine HCl 1%
Glycerol Dioleate 79%
Ethanol 20%

FORMULATION VI-AA Hydroflumethiazide 10%
Glycerol Dioleate 60%
Oleic Acid 10%
Isopropanol 20%

FORMULATION VI-BB Phentermine 5%
Glycerol Trioleate 75%
Propanol 20%

FORMULATION VI-CC Phentermine HCl 10%
Glycerol Monooleate 60%
Ethanol 30%

FORMULATION VI-DD Mazindol 5%
Glycerol Trioleate 75%
Isopropanol 20%

FORMULATION VI-EE Morphine 1%
Methyl Oleate 79%
Isopropanol 20%

FORMULATION VI-FF Morphine Sulfate 5%
Glycerol Monooleate 65%
Oleic Acid 10%
Ethanol 20%

FORMULATION VI-GG Alprazolam 5%
Glycerol Trioleate 75%
Propanol 20%

FORMULATION VI-HH Ibuprofen 10%
Glycerol Trioleate 70%
Isopropanol 20%

FORMULATION VI-II Naproxen Sodium 10%
Glycerol Dioleate 60%
Oleyl Alcohol 20%
Ethanol 10%

FORMULATION VI-JJ Naproxen Sodium 10%
Glycerol Monooleate 70%
Ethanol 20%

FORMULATION VI-KK Progesterone 5%
Methyl Oleate 75%
Isopropanol 20%

FORMULATION VI-LL Methyl Testosterone 5%
Glycerol Trioleate 65%
Isopropanol 30%

Claims

1. A penetration-enhancing pharmaceutical composition for topical application comprising:
(a) about 0.01 to 50% by weight of an active pharmaceutical permeant contained in,
(b) about 40-99.99% by weight of a penetration-enhancing vehicle comprising,
(i) one or more cell-envelope disordering compounds selected from the group consisting of oleic acid, oleyl alcohol, glycerol monooleate, glycerol dioleate and glycerol trioleate and mixtures thereof; and
(ii) a lower alkanol selected from the group consisting of ethanol, propanol and isopropanol and mixtures thereof;
wherein the weight ration of cell-envelope disordering compound to lower alkanol is between about 50:1 and 1:50.

2. A composition according to Claim 1 wherein the ratio of cell-envelope disordering compound to lower alkanol is between about 9:1 and 1:9.

3. A composition according to Claim 2 wherein active pharmaceutical permeant is present in amounts ranging from about 0.01 to 30% by weight and the penetration enhancement vehicle is present in amounts ranging from about 70 to 99.99% by weight.

4. A composition according to Claim 3 wherein the active pharmaceutical permeant is a member selected from the group consisting of antimicrobials, antibacterials, antibiotics, antimyobacterials, antimalarials, antiamebics, anthelmintics, antifungals, antivirals, neoplastic agents, agents affecting the immune response, blood calcium regulators, peptide and protein hormones, male sex hormones, female sex hormones, agents useful in glucose regulation, anticoagulants,, antithrombotics and hemostatics, antihyperlipidemic agents, cardiac drugs, thyromimetic and antithyroid drugs, adrenergics, antihypertensive agents, cholinergics, anticholinergics, antispasmodics, antiulcer agents, skeletal and smooth muscle relaxants, histamine H2-receptor agonists and antagonists, prostaglandins, general inhibitors of the allergic response, antihistamines, local anesthetics, analgesics, antitussives, sedative-hypnotic agents, antidepressant agents, anorexigenics, non-steroidal anti-inflammatory agents, steroidal anti-inflammatory agents, bone-active agents, antiarthritics, vitamins, diagnostic agents, sunscreen agents and compatible mixtures thereof.

5. A composition according to any of Claims 1-4 wherein the cell-envelope disordering compound is oleic acid.

6. A composition according to any of Claims 1-4 wherein the cell-envelope disordering compound is oleyl alcohol.

7. A composition according to any of Claims 1-4 wherein the cell-envelope disordering compound is glycerol dioleate.

8. A composition according to any of Claims 1-4 wherein the cell-envelope disordering compound is a mixture of glycerol dioleate and oleic acid.

9. A composition according to any of Claims 1-4 wherein the cell-envelope disordering compound is glycerol trioleate.

10. A composition according to any of Claims 1-4 wherein the cell-envelope disordering compound is a mixture of glycerol dioleate and oleyl alcohol.

European Patent Office

EUROPEAN SEARCH REPORT

Application Number

EP 87 11 6733

DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.4)
X	EP-A-0 103 783 (THILO) * Page 2, lines 20-26; page 3, line 16 - page 4, line 19; page 5, lines 1-6 *	1-4,6	A 61 K 47/00
X,D	EP-A-0 095 813 (PROCTER & GAMBLE) * Examples 9,10 *	1	
X,D	US-A-4 537 776 (COOPER) * Claims 1,10 *	1	
A	EP-A-0 171 742 (DU PONT NEMOURS) * Tables 1,2,3 *	5,6	
A	EP-A-0 152 281 (YAMANOUCHI) * Claims 1-4 *	1	

TECHNICAL FIELDS SEARCHED (Int. Cl.4)

A 61 K 47/00

The present search report has been drawn up for all claims

Place of search	Date of completion of the search	Examiner
THE HAGUE	26-01-1988	GOETZ G.

CATEGORY OF CITED DOCUMENTS

X : particularly relevant if taken alone
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